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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/579,548 | 05/26/2000 | Alan H. Lazarus | 701826/50750 | 7491 |

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David S Resnick
Nixon Peabody LLP
100 Summer Street
Boston, MA 02110

| EXAMINER | |
|---|---|
| GAMBEL, PHILLIP | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/579,548 | LAZARUS ET AL. | |
| | Examiner | Art Unit | |
| | Phillip Gambel | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *24,27,30 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *24* is/are allowed.

6)☒ Claim(s) *27 and 30* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 9/17/04 has been entered.

Applicant's amendment, filed 9/17/04, has been entered

The numbering of claims is not accordance with 37 C.F.R. 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 CFR 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 24 (new) has been renumbered claim 34 (new).

Claims 1-23, 25-26, 28-29 and 31-33 have been canceled.

Claims 24 and 30 have been amended.

Claim 34 has been added.

Claims 24, 27, 30 and 34 are pending.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 27 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant's arguments have been full considered but are not found convincing essentially for the reasons of record which are reiterated herein for applicant's convenience.

As pointed out previously, given applicant's amended claims limiting the claimed methods to the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1, which has been recognized as a CD40 agonist, the instant methods are subject to the enablement rejection has been set forth herein as it reads on "inhibiting T cell function in an anti-HLA alloimmune response in a patient" (claim 27) and on "preventing a disease selected from the group set forth in claim 30.

As applicant notes, the 18KDa CD40L was known in the part prior to the filing of this application to be a homotrimer (oligomer)in solution, as set forth in Mazzei et al. (J. Biol. Chem. 270: 7025-7028,1995)

Therefore, applicant has amended the claims to limit the soluble CD40L to a known oligomeric CD40L agonist and away from the referenced soluble monomeric CD40L antagonists.

It is acknowledged that the present invention shows that the 18KDa CD40L inhibits a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes which indicates that oligomeric 18 KDa CD40L is an antagonist rather than a CD40 agonist in a platelet HLA alloimmune immunization model.

While applicant submits that the CD40L of the present invention is an oligomeric antagonist, the examiner maintains that the ability of the sCD40L of the instant methods was known as a stimulator of various immunes responses, including B cells responses (e.g. see the Introduction, including page 819, column 1, paragraph 1 of co-inventor's own publication, Lazarus et al., Transfusion 39: 818- 823, 1999), dendritic cell responses and T cell responses (e.g. see entire document, particularly Example 5 in paragraphs [0074] – [0076] of Thomas et al., US 2001/0026932 A1) as well as being recognized as both prothrombotic and proinflammatory (see entire document, particularly the Introduction and Discussion of Nannizzi-Alaimo et al. 105: 2849 –2854, 2002).

It does not appear from the record that the claimed soluble 18 KDa recombinant human CD40L differs from the soluble 18 KDa CD40L / sCD40L of the prior art that has been shown to have properties of stimulating various inflammatory cells and responses. While the claimed soluble 18 KDa recombinant human CD40L may have an beneficial role in inhibiting anti-HLA alloimmune antibody responses numerous, there was insufficient predictability that the soluble 18 KDa CD40L / sCD40L would inhibit any anti-HLA alloimmune response (e.g., transplant rejection) or prevent inflammatory or autoimmunity, broadly encompassed by the claimed methods.

Applicant is correct in acknowledging that an alloimmune response is not necessarily restricted to the production of antibody and may involve T cells.

This is the very reason for one aspect of the rejection of record which is maintained herein in that the claims are not limited to inhibiting anti-HLA alloimmune antibody responses but rather broadly encompasses a number of conditions and diseases wherein the administration of the claimed soluble 18KDa human CD40L would be expected to stimulate or exacerbate immune or inflammatory responses, including anti-HLA alloimune responses, as broadly recited.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs such as costimulatory-based biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the experimental observations of inhibiting a secondary alloimmune response in an SCID experimental model engrafted with human lymphocytes would be predictive of treating the breadth of alloimmune responses, T cell responses, autoimmune diseases encompassed by the claimed methods.

There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit any alloimmune response, T cell responses, autoimmune diseases, commensurate in scope with the therapeutic methods encompassed by the claimed methods.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

As applicant acknowledges, the administration of soluble 18KDa recombinant human CD40L consisting of amino acids 108-261 set forth in SEQ ID NO: 1 has been recognized as a CD40 agonist.

For example, Aruffo et al. (U.S. Patent No. 6,376,459) discloses that treating subject associated with B cell activation comprise administering a ligand such as an antibody that binds CD40CR / CD40L and that CD40CR / CD40L was useful to promote B cell activation (see columns 15-18; Uses of Ligands That Bind to CD40CR and Uses of CD40CR). Here, the therapeutic endpoints and diseases targeted by employing CD40L antagonists and agonists are in direct contrast with the claimed use of soluble 18 KDa CD40L to inhibit cell mediated immune responses, including the use of soluble 18 KDa CD40L in treating or preventing diseases selected from the group set forth instant claim 30.

In addition, Aruffo et al. (U.S. Patent No. 5,540,926) (prior art of record) discloses that soluble gp39 may be used to increase an immune response as a type of adjuvant, while immunosuppression by my accomplished by modifying or linking gp39 with a cytotoxic drug (e.g. see columns 10-11, Utility of the Invention).

Further, Armitage (U.S. Patent No. 6,264,951) (prior art of record) discloses that oligomeric CD40L as agonists, while monomeric CD40L acts as antagonists (e.g. see column 10, paragraphs 2-3). Here, monomeric CD40L antagonists are useful for treating autoimmune diseases encompassed by the claimed methods.

It is noted that Lazarus et al. (Transfusion 39: 818-823, 1999) discloses that the soluble 18 KDa CD40L of the claimed invention cannot inhibit secondary IgG production from memory B cells (see Results, particularly pages 820-821 and Figure 3). Although Lazarus et al. discloses that soluble 18 KDa CD40L could prevent an increase in cell proliferation under certain conditions in a mixed-lymphocyte culture, this 18 KDa CD40L could not inhibit a MLR (see page 821 and Figure 4). Therefore, it appears that the soluble 18 KDa CD40L of the claimed invention may be able to inhibit certain immune responses associated with T cell function and alloimmune responses, soluble 18 KDa CD40L appears limited in the conditions of inhibiting alloimmune responses or T cell immune responses. Also, the Discussion acknowledges that the mechanisms of action by the ability of soluble 18KDa CD40L to inhibit a secondary alloimmune in a SCID mouse engrafted with human lymphocytes is unclear.

Nannizzi-Alaimo et al. (Circulation 105: 2849-2854, 2002) reports that soluble CD40L is a prothrombotic and proinflammatory protein which can contribute to thrombotic and inflammatory complications (See entire document, including Abstract).

In addition, the claims encompass preventing the diseases selected from the group set forth in claim 30. There is insufficient objective evidence that the claimed soluble 18 KDa CD40L can prevent such diseases, including diabetes, arthritis and SLE as set forth in claim 30. For example, the claimed targeted diseases and conditions set forth in claim 30 are treated after the diagnosis of such conditions and diseases.

While given the nature of GVHD wherein the skilled artisan can provide the antagonistic 18Kda human CD40L at the onset of the stimulus for GVHD and, in turn, can prevent GVHD to some extent, prevention of the graft such diseases, including diabetes, arthritis and SLE as set forth in claim 30 with antagonistic 18 KDa human CD40L

There is insufficient objective evidence that one skilled in the art can prevent such autoimmune or inflammatory conditions or diseases as recited in claim 30, much less that one skilled in the art can prevent such conditions or diseases based upon the limited experimental observations based upon the inhibitory properties of 18 KDa human CD40L in alloantibody immunization protocols.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies of inhibiting alloimmune or T cell responses with a known CD40L agonist, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent a sufficient number of working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating or preventing alloimmune or T cell mediated immune responses with the agonistic soluble 18 KDa CD40L employed in the claimed invention.

Applicant's arguments are not found persuasive.

9. Claim 24 is allowed.

Claim 30 would be allowable, if the recitation of "preventing" were to be deleted.

Claim is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims (or to delete the recitation of "preventing" as it reads on all of the diseases set forth in claim 30.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
January 24, 2005